ECX

As an alternative to ECF: For locally advanced (inoperable) or metastatic oesophageal or gastric cancer;
peri-operative use in oesophageal or gastric cancer;
adenocarcinoma of unknown primary

Drugs/Dosage:	Epirubicin	50mg/m^2	IV	D1
	Cisplatin	60mg/m^2	IV	D1
	Capecitabine	625mg/m^2	PO	BD daily throughout treatment

Administration: Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information, provided by Roche, is available via Pharmacy regarding dispersing the tablets for those patients with swallowing difficulties or with feeding tubes.
Epirubicin via fast running infusion of 0.9% Sodium Chloride

Cisplatin: 1 litre 0.9% Sodium Chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 1 litre 0.9% Sodium Chloride IV over 2 hours
1 litre 0.9% Sodium Chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hrs
500ml 0.9% Sodium Chloride IV **or** 500ml - 1 litre water orally over 1 hour

Frequency: 3 weekly cycle
Advanced / metastatic use: up to 6 cycles
All patients for full clinical review after 3 cycles - for locally advanced cases with no other assessable disease, a restaging OGD to assess mucosal response is required after Cycle 3.
Perioperative use: 3 cycles before surgery, plus a further 3 cycles post surgery

Main Toxicities: myelosuppression; alopecia; diarrhoea; mucositis; nephrotoxicity; neuropathy / ototoxicity; palmar-plantar erythema (PPE); cardiomyopathy; cardiotoxicity due to capecitabine (see Comments); ovarian failure/infertility

Anti-emetics: Day 1: highly emetogenic Days 2 – 21: mildly emetogenic

Extravasation: Epirubicin is a vesicant

Regular Investigations:	FBC	D1
	LFTs & U&Es	D1
	Mg^{2+} and Ca^{2+}	D1
	EDTA	Prior to 1st cycle
	MUGA scan	see Comments
	Restaging	after Cycle 3 as indicated (see Frequency)

Comments: Maximum cumulative dose Epirubicin = 950mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, an alternative regimen should be given. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Reason for Update: Restaging requirements added / max no of cycles = 6	Approved by Lead Chemotherapy Nurse: C Palles-Clark
Version: 2	Approved by Consultant: Dr G Middleton
Supersedes: Version 1	Date: 1.4.08
Prepared by: S Taylor	Checked by: S Seymour

Check electrolytes – additional supplementation of magnesium, calcium or potassium may be required.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml Sodium Chloride 0.9% IV +/- furosemide 20 - 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Fluoropyrimidine therapy has been associated with cardiotoxicity (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore, exercise caution in patients with prior history of coronary heart - disease, arrhythmias and angina pectoris.

Dose Modifications

Haematological Toxicity:	Neutrophils $\geq 1.0 \times 10^9$/l and Platelets $\geq 75 \times 10^9$/l	Proceed with treatment, if necessary adjusting epirubicin dose for any previous haematological toxicity as specified below:
	Neutrophils $0.5 – 0.9 \times 10^9$/l or Platelets $50 - 74 \times 10^9$/l	Stop capecitabine and delay treatment until recovery (eg 1 week later). Give full dose cisplatin and 75% dose epirubicin for subsequent cycles. Restart capecitabine at full dose.
	Neutrophils $< 0.5 \times 10^9$/l or Platelets $25 - 49 \times 10^9$/l	Stop capecitabine and delay treatment until recovery (eg 1 week later). Give full dose cisplatin and 50% dose epirubicin for subsequent cycles. Restart capecitabine at full dose.
	Platelets $< 25 \times 10^9$/l	Stop capecitabine and delay treatment until recovery. Omit epirubicin from subsequent cycles. Restart capecitabine and cisplatin at full dose.

If patient suffers an episode of Grade 3 febrile neutropenia at any time, continue after recovery with 25% dose reduction for epirubicin. For any Grade 4 neutropenic sepsis, discuss with Consultant before proceeding with 50% dose reduction for epirubicin.

Renal Impairment:

CrCl (ml/min)	Cisplatin Dose
> 60	100%
50 – 60	75%
40 – 50	50%
< 40	CI (consider ECarboX)

CrCl (ml/min)	Capecitabine Dose
> 50	Give 100% dose
30 – 50	Give 75% dose
< 30	Omit

Hepatic Impairment:

Bilirubin (µmol/l)	Epirubicin Dose
24 - 51	Give 50% dose
52 - 85	Give 25% dose
> 85	Omit

If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

Non-Haematological Toxicities:

Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

Capecitabine toxicities may be managed symptomatically, with modification of the dose (treatment interruption or dose reduction) according to the information below. Once the dose has been reduced, it should not be increased at a later time. Capecitabine doses omitted for toxicity are not replaced or restored.

Capecitabine Dose Adjustment Guidelines for Non-Haematological Toxicities

Common Toxicity Criteria	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose, except if PPE give 85% dose*
Grade 2: 2nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4th Appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose, except if PPE give 70% dose*
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or, with Consultant approval,** interrupt until resolved to Grade 0 – 1	Give 50% dose

* If PPE Grade 2 – 3 occurs for the first time after 10 weeks, interrupt capecitabine. On resolution of toxicity to Grade 0 - 1, capecitabine may be re-introduced with NO dose reduction.

Neuropathy: If patient develops Grade 2 neuropathy or ototoxicity, change from cisplatin to carboplatin. Discuss with Consultant.

References:

Sumpter, K et al; Br J Cancer 2005; 92: 1976-1983 (interim analyses of REAL-2 demonstrating equivalence of capecitabine and 5FU)
Cunningham, D et al; Proc ASCO 2006 Abstract LBA4017 (final results of REAL-2)
Cunningham, D et al; NEJM 2006; 355: 11-20 (peri-operative use of ECF)